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Sustained inflations during delivery suite stabilisation in prematurely-born infants – a randomised trial

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HIGHLIGHTS

- Sustained inflation (SI) versus UK standard practice during initial stabilisation
- Preterm infants were randomised to a 15 second SI or 5 inflations of 2-3 seconds
- The SI group had a shorter time to their first breath
- The SI group had a significantly shorter IPPV duration in the first 48 hours

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ABSTRACT

Background: Sustained inflations at initial stabilisation in the delivery suite may reduce the need for intubation and result in a shorter duration of initial ventilation, but have not been compared to routine UK practice.

Aims: To compare the early efficacy of sustained inflation during stabilisation after delivery to UK practice.

Study design: A randomised trial was performed of a fifteen second sustained inflation compared to five inflations lasting two to three seconds, each intervention could be repeated once if no chest rise was apparent. Respiratory function monitoring was undertaken.

Subjects: Infants born prior to 34 weeks of gestation.

Outcome measures: The minute volume and maximum end-tidal carbon dioxide level in the first minute after the interventions, the time to the first spontaneous breath after the beginning of stabilisation and the duration of ventilation in the first 48 hours.

Results: There were no significant differences in the minute volume or maximum end tidal carbon dioxide level between the groups. Infants in the sustained inflation group made a respiratory effort sooner (median 3.5 (range 0.2 – 59) versus median 12.8 (range 0.4 – 119) seconds, p=0.001). The sustained inflation group were ventilated for a shorter duration in the first 48 hours (median 17 (range 0 – 48) versus median 32.5 (range 0 - 48) hours, p = 0.025). **Conclusions:** A sustained inflation of 15 seconds compared to five two to three second inflations during initial stabilisation was associated with a shorter duration of mechanical ventilation in the first 48 hours after birth.

Key words: resuscitation; premature infants; delivery suite; sustained inflations

Abbreviations: BPD: Bronchopulmonary dysplasia; CPAP: Continuous positive airway pressures; FiO_2: Fraction of inspired oxygen: $ETCO_2$: End tidal carbon dioxide; FRC: Functional residual capacity; NRP: Neonatal Resuscitation Programme; PDA: Patent ductus arteriosus; PEEP: Positive end expiratory pressure; PIP: Peak inspiratory pressure; SI: Sustained inflations

INTRODUCTION

The majority of infants born at less than 34 weeks gestation will require stabilisation at delivery involving the administration of positive airway pressure [1]. There has, however, been a paucity of research into the most effective method of delivering such support, which likely explains the variation in neonatal resuscitation guidelines. In the UK and the Netherlands, the provision of five initial inflations lasting two to three seconds is recommended [2, 3], whereas other countries use the Neonatal Resuscitation Programme (NRP) guidelines, which advise to begin positive pressure ventilation at 40 to 60 inflations per minute [4]. It has been shown that when inflations lasting between one and three seconds were delivered to prematurely-born infants, the time for the infant to make a spontaneous respiratory effort was inversely proportional to the inflation time [5]. In addition, before the first respiratory effort, tidal volumes and end tidal carbon dioxide ($ETCO_2$) levels remained low [6, 7].

There have been several small studies in infants comparing sustained inflations (SIs) to alternative methods of resuscitation. In an early study, a ten second SI compared to initiating ventilation at 40 to 60 inflations per minute (control) was associated with a reduction in the need for intubation, a shorter duration of respiratory support and a reduction in bronchopulmonary dysplasia (BPD) [8]. The SI, however, was delivered via a nasopharyngeal tube and a device capable of delivering positive end expiratory pressure (PEEP), whereas the control intervention was delivered via a bag-valve mask which did not provide PEEP. Two studies comparing results following the introduction of SIs to historical cohorts also found significant reductions in the need for intubation and shorter durations of ventilation [9,10]. An RCT of infants born at less than 33 weeks of gestation found a reduction in the need for ventilation in the first 72 hours with SI followed by nasal continuous positive airway pressure (CPAP) compared to nasal CPAP alone (53% vs 65%, $p = 0.04$)

[11]. In another trial, comparison of an SI to ventilation at 40 to 60 inflations per minute revealed no significant difference in need for intubation at delivery, but a significantly lower oxygen requirement at ten minutes after birth in the SI group [12]. A review of eight studies including 941 infants exposed to inflations of more than one second at resuscitation or inflations of shorter duration found significantly lower durations of mechanical ventilation in the SI arms, but no significant differences in other outcomes [13]. Importantly, there were no significant differences in adverse events, as in one study there had been a concern that SIs might increase the risk of pneumothorax (odds ratio 4**.**57 (95% confidence interval: 0.97-21.50, p=0.06)[11]. Another study, however, reported a non-significant reduction in the rate of pneumothorax with SI (2% versus 11%, p=0.09) [14], but the peak inspiratory pressure (PIP) in the control intervention was up to 40cmH_2O, whereas only 30cmH_2O in the SI group.

There have, however, been no studies comparing the efficacy of SIs to the current UK practice of initially administering five inflations lasting two to three seconds [6]. We hypothesised that a 15 second SI compared to five inflations of two to three seconds would be associated with an earlier first spontaneous breath and hence higher minute volume and maximum end tidal carbon dioxide ($ETCO_2$) levels in the first minute after the intervention during stabilisation in the labour suite and a shorter duration of mechanical ventilation in the first 48 hours after birth.

METHODS

Infants were eligible for randomisation into the study if they were born at less than 34 weeks of gestation between November 2016 and February 2018 and the respiratory function monitoring was available at delivery. The randomised intervention was only delivered if positive pressure delivery was felt by the clinical team to be required. Infants were excluded from the study if a congenital abnormality had been diagnosed antenatally. The trial was

prospectively registered on clinicaltrials.gov with the identifier NCT02967562 and the protocol was published [15]. The study was approved by the Health Research Authority and the London - Riverside NHS Research Ethics Committee to be performed as emergency research without prior informed consent. Posters were displayed in the delivery suite and antenatal ward explaining that all infants born at less than 34 weeks would be enrolled in the study if they needed respiratory support after birth. As soon as possible after admission to the neonatal unit, parents of infants in whom the randomised intervention had been delivered were approached to inform them about the study and to seek consent for retention and analysis of the respiratory function monitoring data. Infants' results were excluded from the analysis if their parents did not consent for retention and analysis of their infant's data.

Infants were randomly allocated using sealed opaque sequentially numbered envelopes either to receive five inflations lasting two to three seconds (as per NLS guidelines) [3] or one fifteen second SI. The allocation sequence was generated and concealed in envelopes by a researcher unconnected with the study. Block randomisation and stratification were not used. The envelopes were kept with the respiratory function monitor and the clinical team were instructed to open the envelope when attending a delivery of a potentially eligible infant, but only to deliver the randomised intervention if the infant required positive pressure delivery. Each intervention could be repeated for a second time if no chest rise was observed at the first attempt. The clinical team were instructed to carry out the rest of the infant's stabilisation according to routine protocol.

Resuscitation protocol and respiratory function monitoring

Stabilisation was performed using a t-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand), using a gas flow rate of 8l/minute. The Neopuff

is a continuous flow, pressure limited device with a built-in manometer, a PEEP valve and maximum pressure relief valve. The maximum pressure relief valve was set at 40 cm H_2O. The initial peak inspiratory pressures used were 20 to 25cmH_2O and the positive end expiratory pressure of 5cmH_2O as per unit guidelines and NLS Guidelines [3]. All infants were initially resuscitated with an inspired fraction of oxygen (FiO_2) of 0.21 (as is used by more than 40% of UK NICUs [16]). The FiO_2 was subsequently increased if necessary to maintain the oxygen saturation levels between 92 and 96%. All those involved had completed a Neonatal Life Support course and had been trained in the use of the respiratory function monitor and the delivery of a sustained inflation. The research team was available to assist with the setting up of the monitoring equipment, but did not contribute to clinical decision making.

Respiratory function monitoring was performed using a NM3 respiratory profile monitor; Philips Respironics, CT, USA). The monitor was connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software (3.0.1.4) (Grove Medical, London, UK) which displayed and recorded the data. The monitor recorded flow, pressure, $ETCO_2$ and tidal volume from a combined flow and carbon dioxide sensor (dead space 0.8ml) that was placed between the Neopuff device and the facemask or endotracheal tube. The sensor comprised a cuvette for non-dispersive infrared mainstream CO_2 detection that also functioned as a fixed orifice pneumotachograph to measure flow. Airway pressure was measured from the proximal pressure-sensing line [17]. Heart rate and oxygen saturations (Masimo SET; Masimo Corporation, Irvine, CA, USA) were recorded from a saturation probe applied to the right wrist. The respiratory function monitoring display was available to the clinical team; the monitors, however, were not in routine clinical use.

The medical records were reviewed and the duration of ventilation in the first 48 hours after birth determined. Infants ventilated for longer than 48 hours, for the purposes of the analysis, were recorded as being ventilated for 48 hours. The duration of ventilation was also recorded as 48 hours, for infants who died in the first 48 hours after birth. We chose the duration of ventilation in the first 48 hours as an outcome, as beyond this the need for ventilation is more likely to be due to other factors, such as sepsis. The results of the first cranial ultrasound scan and whether the infants developed a pneumothorax or bronchopulmonary dysplasia (BPD) were recorded. BPD was diagnosed as per the National Institute of Health consensus definition as a supplementary oxygen requirement for more than 28 days [18]. We report the patent ductus arteriosus (PDA) rate (infants were diagnosed as having a PDA if they required medical or surgical treatment) as in one systematic review [19], more infants treated with SI received treatment for PDA. We also recorded whether infants developed a gastric perforation.

Subsequent to completion of our study, the Sustained Aeration of Infant Lungs (SAIL) study reported a comparison of two SIs of 15 seconds duration to positive pressure ventilation at 40 to 60 inflations per minute [20]. The study was terminated early as there was an excess of mortality in the SI group (7.5 versus 1.4%, p=0.002) [21). We, therefore, also report THE mortality rates in our two study groups.

The respiratory function monitor recordings were analysed to determine the time from the beginning of the five two to three second inflations or SI delivery to when infants made their first spontaneous respiratory effort [19]. Expiratory tidal volumes for each inflation and/or spontaneous breath during the first minute after completion of delivery of the randomised interventions were measured and the minute volume calculated. The maximal $ETCO_2$ levels in the first minute of monitoring after delivery of the randomised intervention were also determined.

Sample size

We have previously shown that the time to the first spontaneous breath was shorter and the expiratory tidal volume was higher in infants who received longer compared to shorter inflation durations [5]. We, therefore, postulated that the total expiratory minute volume in the first minute following the randomised intervention would be 25% higher in the SI group. In a previous study, the standard deviation of the minute volume was 71 mL/min/kg, which was 25% of the maximum minute volume achieved [6]. Recruitment of 40 infants allowed detection of that difference with 90% power at the 5% significance level. After recruitment of 40 infants, there were, however, significant differences in the demographics of the two groups and therefore a substantial amendment to increase the sample size to sixty was submitted to and approved by the Research Ethics Committee.

Statistical analysis

Data were assessed for normality using a Kolmogorov-Smirnoff test and found not to be normally distributed. Therefore, the Mann Whitney-U test and the Chi squared test were used to assess whether differences were statistically significant as appropriate. Infants' results were analysed according to intention to treat. Analysis was performed using IBM SPSS Statistics for Windows version 24.

RESULTS

One hundred and sixty-six potentially eligible infants were born in the study period, 60 infants were included in the trial (Figure 1). There were no statistically significant differences between those infants who were included or not included in the study regarding gestational age or birth weight (median GA 30.3 (23.1 – 33.3) weeks versus 29.1 (23.6 – 33.4) weeks,

p=0.63; median birth weight 1150 (538 - 2260) grams versus 1346 (550 - 2575) grams, p=0.30). The results of two infants could not be used due to very high leak throughout the recordings rendering analysis impossible. In another infant, parental consent was not obtained for analysis of the data and hence the infant's results were not included in the analysis. One infant randomised to the SI group received an SI followed by two sets of IB; this infant's results were analysed as part of the SI group. There were no significant differences in the demographics and initial resuscitation pressures between the two randomised groups (Table 1). The median duration of the sustained inflations was 15.9 (range 9.2 – 22.1) seconds and the durations of "two to three second" inflations was 1.98 range (0.86 – 4.3) seconds. Ten infants had a second sustained inflation and six had a second round of five two to three second inflations (p=0.24).

The time to the first breath from the beginning of the five two to three second inflations or SI delivery was significantly shorter in those infants who received a sustained inflation (Table 2). There were no significant differences in the minute volume or maximum $ETCO_2$ levels between the two groups. Twenty-four infants in the SI group (80%), and 27 infants in the IB group (90%) were ventilated on the NICU (p=0.28), but infants who received an SI were ventilated for a significantly shorter period of time in the first 48 hours (Table 2). There were no significant differences between the two groups regarding the development of BPD (40% in the SI group versus 63% in the IB group, p=0.08), or pneumothorax (n=0 in the SI group, n=1 in the IB group, p=0.31) or IVH (21% in the SI group, 20% in the IB group, p=0.84), but significantly fewer infants required medical or surgical treatment for a PDA in the SI group (7% versus 29%, p=0.036.) No infant in the study developed gastric perforation. Three infants in the IB and two in the SI group died (p=0.64). Both infants in the SI group developed severe multiorgan failure in the first 48 hours after birth following adverse antenatal events. In the IB group, one infant died on day one due to hypoxic respiratory failure, intensive care was withdrawn on day four in another due to severe intracranial

haemorrhage and multiorgan failure and the other infant died from late onset sepsis. There was no significant difference between the two groups in mortality in the first 48 hours after birth (p=0.55).

DISCUSSION

We have demonstrated that prematurely born infants who required stabilisation at delivery made their first spontaneous respiratory effort sooner if they received a sustained inflation compared to five inflations each lasting two to three seconds. Additionally, the infants who received a sustained inflation were mechanically ventilated for a significantly shorter time in the first 48 hours after birth compared to those who received five two to three second inflations. Sustained inflations have been previously shown to be associated with a reduction in the need for mechanical ventilation in the first few days after birth, but comparison was made to different control interventions. Three SIs versus bag valve mask ventilation at 40 to 60 breaths per minute were associated with a reduction in the need for mechanical ventilation within 72 hours of birth (odds ratio 2.56, (95% confidence interval 1.15 – 5.7) [14]. Pooled analysis of four other studies also demonstrated a reduction in the need for mechanical ventilation within 72 hours with sustained inflations (relative risk 0.87 (95% confidence interval 0.77 to 0.97)) [18]. Amongst infants born at less than 34 weeks of gestation, the proportion requiring ventilation was lower (14%) with an SI at 25cmH_2O than the proportion who received inflations at 60 per minute, with the initial inflation pressure of 30-40cmH_2O followed by subsequent inflations at 20cmH_2O (55%) ($p<0.01$) [9]. In addition, the total duration of ventilation was shorter in the SI group (9.1 days versus 13.8 days, $p\leq0.001$). The SAIL study reported an excess of mortality in the sustained inflation group, hence the study was terminated prematurely [21]. The SAIL study recruited infants born between 23 and 27 weeks of gestation, whereas in this study infants were recruited if less than 34 weeks of gestational age. Furthermore, the control arms in the two studies differed.

We did not report an excess of mortality, but emphasize our study was not powered to detect a significant difference in mortality.

There are strengths and some limitations to our study. It is the first randomised trial comparing the UK standard practice of five inflations lasting two to three seconds to a sustained inflation. The use of respiratory function monitoring allowed us to determine the time taken for infants to make a spontaneous respiratory effort after the onset of stabilisation. We did not stratify our groups which in hindsight would have been helpful. Indeed, we had to increase our sample size, as after forty infants there were significant differences in the demographics between our two groups. Many of the five two to three second inflations were shorter than the recommended duration as has been previously reported [6, 22], but this meant we were comparing current UK practice to the use of a sustained inflation and hence our results are generalisable. We recorded the occurrence of BPD, PDA and gastric perforation, but our study was not powered to detect significant differences in those outcomes. We display the data to give more clinical information about the study population.

In conclusion, a sustained inflation lasting fifteen seconds compared to five repeated inflations lasting two to three seconds during initial stabilisation at delivery of infants born at less than 34 weeks of gestation was associated with a shorter time to the first breath and a shorter duration of mechanical ventilation in the first 48 hours after birth. Our results then demonstrate a SI was more efficacious in the short term, but whether this translates to improved long term outcomes now needs assessing in an appropriately designed study.

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Table 1. Demographic details and initial resuscitation pressures by resuscitation mode

Data are presented as median (range) or n (%)

	Sustained Inflations	'Inflation Breaths'	p
n	30	30	
Gestational age (weeks)	30.6 (24.0 – 33.7)	29.7 (23.1 – 33.6)	0.15
Birth weight (grams)	1243 (632 – 2260)	1001 (538 – 1738)	0.07
Antenatal corticosteroid exposure	27 (90)	24 (80)	0.28
Postnatal surfactant administration	24 (80)	27 (90)	0.28
Vaginal delivery	12 (40)	9 (30)	0.42
Initial resuscitation pressures:			
Peak inspiratory pressure (cmH_2O)	26.2 (19.6 – 29.6)	26.1 (14.7 – 31.0)	0.88
Positive end expiratory pressure (cmH_2O)	5.1 (2.8 – 6.5)	4.9 (2.0 – 8.6)	0.28

Table 2. Outcomes by resuscitation mode

Data are presented as median (range)

	Sustained Inflations	'Inflation Breaths'	p
n	30	30	
Time to first spontaneous breath (seconds)	3.5 (0.2 – 59)	12.8 (0.4 – 119)	0.001
Minute volume in the first minute (ml/kg/min)	196 (45 – 505)	153 (18 – 385)	0.21
Maximum end tidal CO_2 (mmHg)	34.2 (1.4 – 80.5)	28.6 (1.9 – 46)	0.07
Duration of ventilation in first 48 hours for all infants (hours)	17 (0 – 48)	32.5 (0 – 48)	0.025
Duration of ventilation in the first 48 hours of those who were ventilated (hours)	19.5 (5 – 48)	48 (5 – 48)	0.031

FIGURE LEGEND

Figure 1: Consort diagram of recruitment